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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,326	06/14/2001	David B. Rozema	Mirus.013.02	1467

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/881,326	Rozema et al.
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 12, 2003*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 12, 2003 has been entered.

Status of the Claims

2. Claims 1-3 are pending.

3. Claims 1-3 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-19 of U.S. Patent No. 6,383,811 in view of US 5,698,531. Applicants have indicated that a terminal disclaimer will be filed upon notice of allowability of the instant claims.

4. Claim 1 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 09/447,966. Applicants have indicated that a terminal disclaimer will be filed upon notice of allowability of the instant claims.

5. Claim 1 stands rejected under 35 U.S.C. 102(b) as being anticipated by US 5,698,531 (Nabel et al.). Response to arguments in Paper No. 14, filed May 12, 2003 follows the repeated rejection below.

6. Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,698,531 (Nabel et al.) in view of US 2001/0005717 A1 (Wagner et al.). No arguments have been made regarding this rejection, instead there is a reliance upon the arguments of the rejection of claim 1 under 35 USC 102.

Response to Arguments

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-19 of U.S. Patent No. 6,383,811 in view of US 5,698,531. Claims 13-19 of U.S. Patent No. 6,383,811 are drawn to a process of delivering a polynucleotide to a blood vessel and then to an extravascular cell. The polynucleotide is delivered in a complex comprising the polynucleotide and a cationic polymer (such as PEI) where the charge on the complex is less negative than the charge on the polynucleotide, then expressing the polynucleotide in the extravascular cell. Claims 1-3 of the instant claimed invention are drawn to a process of delivering a polynucleotide/polymer complex which has a zeta potential less negative than the polynucleotide to an extravascular parenchymal cell, increasing the permeability of the blood vessel and expressing the polynucleotide in the parenchymal cell. The polycation may have a pKa of 5-7 and the polymer may consist of imidazole groups, pyridine groups or aniline groups.

The instant specification states that PEI is a polymer which is well known in the prior art to have a pKa in the range of 5-7 at physiological pH. US 5,698,531 taught (see especially the abstract and columns 4-7) the obvious and desirable increasing of the permeability of a vessel to

deliver a polynucleotide complex to the extravascular cells (parenchymal cells, as defined in the instant specification), making increasing the permeability of a vessel to deliver a polynucleotide complex to an extravascular parenchymal cell obvious.

9. Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 09/447,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-5 of copending Application No. 09/447,966 are drawn to a process of delivering a polynucleotide to an extravascular parenchymal cell where the polynucleotide is in a complex with an amphipathic compound, inserting the complex into a blood vessel, increasing the permeability of the blood vessel to deliver the polynucleotide to an extravascular parenchymal cell and expressing the polynucleotide in the parenchymal cell. Claim 1 of the instant claimed invention is drawn to a process of delivering a polynucleotide in a complex with a polymer where the complex has a zeta potential less negative than the polynucleotide into a blood vessel, increasing the permeability of the blood vessel, delivering the complex to an extravascular parenchymal cell and expressing the polynucleotide in the parenchymal cell.

The instant specification states that PEI is a polymer known in the prior art which may be used to form the instant claimed polymer complex, and further states that PEI is an ampholite which is known in the prior art to have a pKa in the range of 5-7 at physiological pH.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by US 5,698,531 (Nabel et al.).

Nabel et al. taught (see especially the abstract and columns 4-7) a process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal by mixing the polynucleotide and the polymer to form a complex, wherein the zeta potential of the complex is less negative than that of the polynucleotide alone at physiological pH. The complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and the polynucleotide is expressed.

Response to Arguments

12. Arguments set forth in Paper No. 14 at page 2 assert that a statement made by "Nabel (1995)" regarding the delivery of DNA to "cells beyond the blood vessel" is an indication that

delivery as taught in US 5,698,531 "fails to reach even the outermost layer of the blood vessel and thus cannot be reasonably interpreted to mean delivery to extravascular cells". The argument continues to assert that the method fails to achieve delivery to extravascular parenchymal cells by a recitation of an excerpt from an amendment filed in the prosecution of US 5,698,531 on November 22, 1993, where recombinant gene delivery to vascular cells is discussed. The statement is characterized as indicating "that the transformed cells are restricted not only to cells of the arterial wall, but to cells of a very localized section of the arterial wall...a section delimited by the balloon catheters".

In the specification of the '531 patent, at column 3, lines 51-57, column 4, lines 12-24, lines 37-50, column 5, lines 15-14, column 6, line 43 to column 7, line 39, and the claims, specific teachings are found on the process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal. At column 4, lines 12-24 and lines 37-50 Nabel et al. teach that the complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and the polynucleotide is expressed. Therefore, the argument is not found convincing.

The statement and arguments do not negate the very clear teachings of US 5,698,531 on delivery of polynucleotides to extravascular parenchymal cells found at column 3, lines 51-57, column 4, lines 12-24, lines 37-50, column 5, lines 15-14, column 6, line 43 to column 7, line 39, and the claims. The cited publication is irrelevant to the issue of enablement of the teachings of

the patent. The patent is issued on its own merits and strengths. The excerpt from the prosecution history of US 5,698,531 does not address the delivery of a polynucleotide to parenchymal cells as taught at the cited passages above. Therefore, the arguments are not found convincing.

13. It is further argued in Paper No. 14, pages 2-3, that there is no guidance, and that no specific teachings are provided on the delivery of a polynucleotide to a parenchymal cell.

In the specification of the '531 patent, at column 3, lines 51-57, column 4, lines 12-24, lines 37-50, column 5, lines 15-14, column 6, line 43 to column 7, line 39, and the claims, specific teachings are found on the process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal. At column 4, lines 12-24 and lines 37-50 Nabel et al. teach that the complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and the polynucleotide is expressed. Therefore, the argument is not found convincing.

14. It is asserted in Paper No. 14, page 3 that this examiner holds the position that "because Nabel does not specifically state that extravascular cells are not targeted, the method of Nabel teaches delivery to extravascular cells."

On the contrary, the position held by this examiner is that Nabel et al. teach the delivery of a polynucleotide to parenchymal cells as taught in the specification of the '531 patent, at column 3, lines 51-57, column 4, lines 12-24, lines 37-50, column 5, lines 15-14, column 6, line

43 to column 7, line 39, and the claims, specific teachings are found on the process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal. At column 4, lines 12-24 and lines 37-50 Nabel et al. teach that the complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and the polynucleotide is expressed. Therefore, the argument is not found convincing.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,698,531 (Nabel et al.) in view of US 2001/0005717 A1 (Wagner et al.).

The claims are drawn to a process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal by mixing the polynucleotide and the polymer to form a complex, wherein the zeta potential of the complex is less negative than that of the polynucleotide alone at physiological pH. The complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and

the polynucleotide is expressed. The polymer may have at least one functional group with a pKa in the range of 5-7 and may consist of imidazole, or pyridine or aniline groups.

Nabel et al. taught (see especially the abstract and columns 4-7) a process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal by mixing the polynucleotide and the polymer to form a complex, wherein the zeta potential of the complex is less negative than that of the polynucleotide alone at physiological pH. The complex is delivered into a mammalian vessel *in vivo*, the permeability of the vessel is increased by increasing the pressure in the vessel, the complex passes through the vessel into the extravascular parenchymal cells and the polynucleotide is expressed.

Nabel et al. did not teach that the polymer may have at least one functional group with a pKa in the range of 5-7 and may consist of imidazole, or pyridine or aniline groups.

Wagner et al. taught (see especially paragraphs 49-55, example 13 and figure 14) a process of delivering a polynucleotide complexed with a polymer which has functional groups with a pKa in the range of 5-7 consisting of imidazole groups and transfecting the polynucleotide through a vessel into the surrounding tissues (parenchyma) of the vessel where the permeability of the vessel has been increased.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the method of introducing a polynucleotide into parenchymal cells surrounding a blood vessel of Nabel et al. with Wagner et al. which teaches the use of a polymer which has functional groups with a pKa in the range of 5-7 consisting of imidazole

groups to increase the efficiency of the transfection. One of ordinary skill in the art would have been motivated to combine the teachings of Nabel et al. and Wagner et al. for the expected benefit of increasing the permeability of the blood vessel and increasing the efficiency of transfection, thereby increasing the delivery of the polynucleotide to the parenchymal cells surrounding the blood vessel. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Nabel et al. who demonstrate the delivery of a polynucleotide to a parenchymal cell surrounding a blood vessel and the teachings of Wagner et al. who demonstrate the increased efficiency of delivery of a polynucleotide to the parenchymal cells surrounding the blood vessel.

Conclusion

17. This is a continuation of applicant's earlier Application No. 09/881,326. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61

(November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
June 27, 2003

JAMES KETTER
PRIMARY EXAMINER

JAMES KETTER
PRIMARY EXAMINER